REMARKS

In the Claims:

Claims 1-105 are cancelled. Claims 106-134, 136, and 138-141 are amended herein. New claims 143-146 are added herein.

Amendment of claims 106-108, 110-114, 117-134, 136, and 138-141 relates to form and/or grammar and is made only for the purpose of increasing the clarity of these claims. No new matter is added by amendment of claims 106-108, 110-114, 117-134, 136, and 138-141.

Amendment of claims 109, 115, and 116 is only for the purpose of increasing the clarity of these claims. In particular, claim 109 is amended herein to clarify that the protein introduced in a mammal according to the method of claim 106 is selected from the group consisting of tissue plasminogen activator, urokinase, streptokinase, transforming growth factor alpha, transforming growth factor beta, angiogenin, tumor necrosis factor alpha, tumor necrosis factor beta, acidic fibroblast growth factor, and basic fibroblast growth factor. No new matter is added by this amendment and support for the amendment may be found at pages 27 and 30 of the specification.

Claim 115 is amended herein to clarify that the method of claim 115 is used to treat an ischemic condition in a human patient, and that the method comprises the step of site-specific instillation of transformed cells into the patient. No new matter is added by this amendment and support for the amendment may be found at pages 10 and 27 of the specification.

Claim 116 is amended herein to clarify that the transformed cells used in the method of claim 115 include an exogenous nucleic acid that encodes a protein selected from the group consisting of tissue plasminogen activator, urokinase, streptokinase, transforming growth factor alpha, transforming growth factor beta, angiogenin, tumor necrosis factor alpha, tumor necrosis factor beta, acidic fibroblast growth factor, and basic fibroblast growth factor. No new matter is

added by this amendment and support for the amendment may be found at pages 27 and 30 of the specification.

New claim 143 is directed to a method of introducing a protein in a mammal, comprising delivering to a blood vessel in the mammal a transformed vascular cell, wherein the transformed cell (i) originates from the mammal or is syngeneic to the mammal, and (ii) comprises an exogenous nucleic acid encoding the protein. No new matter is added by this claim, which is supported at pages 31-41 of the specification. New claim 144 is directed to the method of new claim 143, wherein the transformed cell expresses the protein in the mammal. No new matter is added by this claim, which is supported at pages 31-41 of the specification, and by currently pending claim 106. New claim 145 is directed to the method of new claim 143, wherein the transformed cell attaches to the wall of the vessel in the mammal. No new matter is added by this claim, which is supported at pages 31-41 of the specification, and by currently pending claim 107. New claim 146 is directed to the method of new claim 143, wherein the transformed cell is an endothelial cell or a smooth muscle cell. No new matter is added by this claim, which is supported at page 31-41 of the specification, and by currently pending claim 108.

35 U.S.C. § 112, first paragraph – Enablement

Claims 109-142 stand rejected under 35 U.S.C. § 112, first paragraph, for alleged lack of enablement. The Office action states three bases for this rejection. First, the Office action states that there is lack of enablement for treating a disease by implanting into a mammal or human a cell transformed to express a protein, wherein expression of the protein achieves a therapeutic effect. Second, the Office action states that the claims are overly broad. Specifically, the Office action states, "in view of the substantial differences between diseases such as diabetes, liver disease, and injury-induced neointimal hyperplasia, the art-recognized unpredictability in achieving therapeutic levels of gene expression *in vivo* capable of treating a disease, and the breadth of the claims, it would have required undue experimentation to practice the scope of the

invention as claimed." (Office Action mailed Aug. 25, 2004). Third, the Office disputes the relevancy of the references cited by Applicants as further evidence demonstrating that the present invention is enabled. Specifically, the Office action states that "[t]aken as a whole, none of the references cited by the applicants exemplifies the instant methods as claimed, or teaches that the implantation of transformed vascular cells would be capable of expressing sufficient levels of a therapeutic protein for a sufficient length of time to treat any disease in any mammal, including a human." (Office action mailed Aug. 25, 2004, p. 7). Applicants respectfully disagree.

To overcome an enablement rejection, an applicant is required to demonstrate, by argument or other evidence, that the disclosure *as filed* would have enabled the claimed invention. *See MPEP* § 2164.05. The MPEP explicitly allows for an applicant to provide a declaration after the filing date to demonstrate that the claimed invention works. According to the MPEP, when an applicant submits such a declaration, "the examiner should carefully compare the steps, materials, and conditions used in the experiments of the declaration with those disclosed in the application *to make sure they are commensurate in scope.*" MPEP § 2164.05 (emphasis added). There is no requirement in the MPEP that the steps, materials, and conditions used in the experiments described in the inventor declaration be *the same as* the steps, materials, or conditions disclosed in the specification.

On July 30, 2003, Applicants submitted the Declaration of Elizabeth G. Nabel, M.D., (hereinafter the "Nabel Declaration"), in accordance with the requirements of MPEP § 2164.05. The Nabel Declaration recites the successful application of the claimed method as described at pages 14-16 of the specification. *See* Nabel Declaration, paragraph 5. Specifically, at paragraphs 7-10, the Nabel Declaration describes using the following procedures to demonstrate that implanting a cell transformed to express the p27 protein into a mammal, using the methods claimed herein, achieves a therapeutic effect:

> 7. Four pigs, two as a control group and two as an experimental group, were used. In each pig, VSMCs were isolated from a peripheral vein and grown in cell culture. The cultured VSMCs from two pigs were transformed with an adenoviral vector expressing p27, a cell cycle inhibitor protein (Adp27). The cultured VSMCs from the two control pigs were transformed with a control adenoviral vector that does not express a biologically active protein (AdCo). Four days after transformation, the cells were examined by immunostaining for p27 and Western blotting and confirmed that the Adp27 cell lines expressed p27 and the cell lines in the control group did not.
>
> 8. Thereafter, the transformed VSMCs were site-specifically instilled into the pigs. Each of the four pigs was anesthetized and the two femoral arteries were exposed. A balloon angioplasty catheter was introduced into each femoral artery, and the balloon was inflated to create a vascular injury. Following vascular injury of each artery, each arterial segment was flushed with saline, and 4.5 x 10^6 transformed VSMCs were instilled therein at the site of injury. The transformed VSMCs originated from the pigs in which they were implanted.
>
> 9. The pigs were allowed to recover for three weeks. Following the recovery period, the pigs were anesthetized, the arterial segments were removed from each pig, and the pigs were euthanized. The arterial segments were fixed and analyzed.
>
> 10. Analysis of the arterial segments revealed that the two experimental pigs, with VSMCs expressing p27, had a significant reduction in intimal hyperplasia and arterial lesion development as compared to the two control pigs.

Paragraphs 7-10 of the Nabel Declaration, submitted July 30, 2003.

However, the data set forth in the Nabel Declaration was not considered because, according to the Office action, p27 was not known as of the priority date of the present invention, i.e., 1989. Implicitly, the Office action has elected to ignore data that explicitly demonstrates enablement of claims 109-142 because the data were generated with respect to a gene and gene product (p27) identified later than the filing date of this application. This position inexplicably implies that the p27 data cannot be relied on to show enablement of *method*

claims 109-142 even though the methods and materials employed were all as set forth in the instant specification in all other respects, as just discussed.

Applicants know of no reason why one of ordinary skill in the art, either at the time the application was filed or now, would expect the protein p27 to behave differently than any of the earlier-known proteins that were recited in the specification as being usefully employed with the claimed method. Thus, p27 is a material that is *commensurate in scope* with any other protein that might be used in practicing the claimed method. Moreover, the broadest claimed method is not limited to use with any specific protein. Therefore, in demonstrating that the *claimed* invention is enabled, Applicants are neither required to use, nor limited to using, only those proteins disclosed in the specification, or those known in the art at the time the application was filed.

Not only the MPEP, but the courts as well, recognize that post-filing evidence is relevant to enablement, if it proves that the invention works. *See Quigg v. Gould,* 822 F.2d 1074, 1078, 3 USPQ2d 1302, 1305 (Fed. Cir. 1987). Here, the invention is the method, not the gene or the encoded protein generated following the steps of the inventive method, thereby lending strength to Applicants' assertion that the identity of the protein used is immaterial to the question of enablement of the method claims.

Further, Applicants have herein clarified claims 109, 115, and 116. In particular, Applicants have clarified claims 109 and 116 by amending these claims to state that the protein introduced in a mammal according to the methods of claims 109 or 116 is selected from the group consisting of tissue plasminogen activator, urokinase, streptokinase, transforming growth factor alpha, transforming growth factor beta, angiogenin, tumor necrosis factor alpha, tumor necrosis factor beta, acidic fibroblast growth factor, and basic fibroblast growth factor. Applicants have amended claim 115 herein to clarify that the method of claim 115 is used to treat an ischemic condition in a human patient, and that the method comprises the step of site-specific instillation of transformed cells into the patient. Thus, as clarified, the so-amended claims do not read on the expression of any

recombinant protein by vascular cells implanted into a host mammal, or the treatment of any disease in a human patient. Rather, the amended claims are directed to methods for treating ischemic conditions using one of the therapeutic proteins disclosed in the specification at page 27 or 30.

"The scope of enablement must only bear a 'reasonable correlation' to the scope of the claims. *See, e.g., In re Fisher,* 427 F.2d 833,839, 166 USPQ 18, 24 (CCPA 1970)." MPEP § 2164.08. Applicants have enabled treatment of ischemic conditions using the claimed methods and therefore, the scope of enablement is commensurate with the scope of the claims.

Specifically, at pages 2-5, the specification describes the etiology and pathogenesis of ischemic conditions. At pages 27 and 30-36, the specification explains that atherogenesis, an ischemic condition with similar characteristics in swine and humans, can be treated using the claimed methods. In particular, pages 31-36 of the specification describe using the claimed methods to achieve stable expression levels of a marker gene for up to six weeks after cells transformed to express the marker gene were instilled into a porcine artery. Pages 27 and 30 set forth various non-marker proteins that might be used with these methods to achieve treatment of an ischemic condition. The Nabel Declaration provides evidence that non-marker proteins can be used with the claimed methods to achieve treatment of an ischemic condition. In particular, the Nabel Declaration provides evidence that the p27 protein can be used with the claimed methods to treat the ischemic condition intimal hyperplasia.

Thus, the specification enables one of ordinary skill in the art to practice the claimed methods for treating an ischemic condition. This scope of enablement is sufficient to satisfy the enablement requirement of 35 U.S.C. § 112, first paragraph. Indeed, "[a]s concerns the breadth of a claim relevant to enablement, the only relevant concern should be whether the scope of enablement provided to one skill in the art by the disclosure is commensurate with the scope of protection sought by the claims. *AK Steel Corp. v. Sollac,* 344 F.3d 1234, 1244, 68 USQP2d 1280, 1287 (Fed. Cir. 2003)."

Additionally, Applicants respectfully disagree with the Office's objection to Applicants' reliance on references cited by Applicants in the Response and Request for Reconsideration mailed May 25, 2004. Applicants maintain that under *In re Strahilevitz,* 668 F.2d 1229, 212 USPQ 561 (CCPA 1982), art references may be cited by Applicants and may be considered in combination with the specification, to demonstrate that the specification enables one of ordinary skill in the art to practice the claimed invention. Applicants rely on these references, not for the reasons stated in the Office action, but only as additional evidence that cells transformed to express a therapeutic protein, which achieve expression of that protein in the vicinity of proliferating neointimal cells, exert a therapeutic effect.

At least for the reasons stated above, the claims as amended herein are not overly broad and undue experimentation would not be required to practice the full scope of the invention as claimed. Applicants have overcome the bases for rejecting the presently pending claims for alleged lack of enablement. Therefore, Applicants respectfully request this ground of rejection be withdrawn.

If, however, the Office maintains the enablement rejection, then pursuant to 37 C.F.R. § 1.104(d)(2), Applicants respectfully request that the Examiner submit an affidavit to inform Applicants of the reason or reasons by which the Examiner has concluded that the assertions in the Nabel Declaration are invalid, untrue, or reasonably ignored. Applicants' position is simply this: The p27 data set forth in the Nabel Declaration plainly prove that the claimed method actually works in accordance with the teaching of the specification and, therefore, the claimed invention is enabled; that p27 was the gene and gene product used to demonstrate enablement is immaterial as it is not an element of the claims in question.

Double Patenting

The Examiner maintains that the rejection of claims 106-109, 114-118, 121-131, 136, and 142 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 8-14 of U.S. Patent No. 6,203,991.

Applicants respectfully disagree with this ground of rejection, but as stated previously, to expedite allowance of the pending claims, Applicants will file a terminal disclaimer upon the allowance of the rejected claims.

CONCLUSION

Pending claims 106-142 are patentable. Applicants respectfully request the Examiner grant allowance of these claims. The Examiner is invited to contact the undersigned attorney for Applicants via telephone if such communication would expedite allowance of these claims.

Respectfully Submitted,

C. Noel Kaman

C. Noel Kaman
Reg. No. 51,857
Attorney for Applicant

BRINKS HOFER GILSON & LIONE
P.O. BOX 10395
CHICAGO, ILLINOIS 60610
(312)321-4200